UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,693	05/23/2001	W. Robert Arathoon	P1099R1C1	1782

23552 7590 03/16/2005

MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,693	ARATHOON ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 17, 2004 has been entered.

2. The amendment filed December 17, 2004 is acknowledged and has been entered. Claims 30-51 have been canceled. Claims 52-87 have been added.

3. Claims 52-87 are pending in this application and are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following Office action contains NEW GROUNDS of objection and rejection necessitated by amendment.

New Grounds of Objection

6. Claims 82-87 are objected to because claim 82 recites, "[a] method for preparing a bispecific antibody comprising: (a) a variable light chain [...]; (b) culturing a host cell [...]; and (c) recovering the bispecific antibody". The body of the claim appears to recite active steps, since (b) and (c) list the steps of culturing a host cell and recovering the bispecific antibody, respectively; however, the language set forth under (a) is not an active step and instead appears to describe the bispecific antibody produced by the process. The claim is therefore constructed in an inconsistent and possibly ambiguous manner. Appropriate correction is required.

7. Claim 86 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 86, which depends from claim 82, recites, "wherein the antibody variable light chain has at least 98% sequence identity to each variable light chain domain of a first and second antibody", but claim 82 recites, "the variable light chain [has] at least 98% sequence identity to each variable light chain domain of a first and second antibody" in lines 3-5. Accordingly, claim 86 does not further limit the subject matter of claim 82.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 52-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 52-65 are indefinite because claims 52, 56, 58, and 64 recite, "each variable light chain is selected to have a common sequence". There is insufficient antecedent basis in the claims to support this recitation because the preceding claim language only recites "a variable light chain". Were the preceding claim language to provide sufficient antecedent basis for the recitation of "each variable light chain", there would necessarily have to be a prior recitation of *a plurality* of variable light chains.

10. Claims 52-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description rejection".

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Claims 52-54, 58-63, 66-71, 74-79, and 82-87 are drawn to methods for producing a bispecific antibody comprising culturing a host cell comprising a nucleic acid encoding the bispecific antibody and recovering the bispecific antibody; claims 56, 57, 64, 65, 72, 73, 80, and 81 are drawn to host cells comprising nucleic acid encoding a bispecific antibody.

Claims 52-57, 66-68, 72 are directed to a genus of bispecific antibodies that comprise a plurality of variable light chain polypeptides that have "a common sequence" but interact with a first and a second antibody heavy chain polypeptide to form an antigen-binding domain for a first and a second antigen, respectively.

The specification describes the term "a common amino acid sequence" at page 21, line 27, through page 22, line 24. For example, the specification describes the common amino acid sequence of the light chain to be "a sequence designed to be an approximation" of two compared light chain sequences of two antibodies against two different antigens; see page 22, lines 9 and 10. Thus, the light chain polypeptide of which the bispecific antibody is comprises is not necessarily identical to one or the other light chains to which the comparison is made and in fact may differ. Most notably, the light chain polypeptides of which the bispecific antibody is comprised may differ at positions within any one of the three complementarity-determining regions (CDRs).

Furthermore, the bispecific antibody produced by the claimed invention does not necessarily retain the binding specificities of these two antibodies against the two different antigens; so, the claims embrace bispecific antibodies having any binding

specificity that may be produced from culturing a host cell comprising a nucleic acid molecule encoding a bispecific antibody comprising a light chain having a sequence that is "an approximation" of two antibodies having known specificities.

Nevertheless, because by definition the bispecific antibody binds two different antigens, the light chains of which the antibody is comprised necessarily function differently, regardless of their structural commonality or lack thereof.

Accordingly, claims 52-57 and 66-72 are directed to a genus of bispecific antibodies having nondescript and varying binding specificities that comprise a genus of variable light chain polypeptides that differ structurally and functionally.

Because the members of the variable light chain polypeptides differ both structurally and functionally, there is no correlation between any one particularly identifying and substantial structural feature and any one particularly identifying functional feature (e.g., binding specificity). Therefore, absent a detailed description of at least a substantial number of the members of the genus of variable light chain polypeptides that have a common sequence but function differently, the supporting disclosure would not reasonably convey to the skilled artisan that Applicant has possession of the claimed invention.

Claims 58-60, 62-65, 74-76, 78-84, 86, and 87 are directed to a genus of bispecific antibodies that comprise at least one of a plurality of variable light chain polypeptides are at least 98% identical to each other or that have are at least 98% identity to the light chain polypeptides of a first and second antibody that bind a first and a different second antigen.

Claims 82-84, 86, and 87 recite that a light chain polypeptide of the bispecific antibody is at least 98% identical to each light chain polypeptide of two different antibodies having unique binding specificities but may otherwise differ at any position, including those positions within the CDRs.

Notably, claims 58-60, 62-65, 74-76, and 78-81, reciting that the light chain polypeptides of the bispecific antibody are 98% identical to each other or 98% identical to both the light chain polypeptides of two different antibodies having unique binding specificities and in either event, *differ from one another at amino acid positions outside*

the CDRs, do not require the light chains to comprise the same CDRs, since the light chain polypeptides may still vary within the CDRs. In other words, these claims do not recite that the light chain polypeptides vary from the others *only* at positions outside the CDRs and therefore may vary within the CDRs.

Were claims 58-60, 62-65, 74-76, 78-84, 86, and 87 to recite that the light chain polypeptides of the bispecific antibodies differ only at positions outside the CDRs, the written description requirement would still not be met. Because the light chain polypeptides of which the bispecific antibody bispecific antibody is comprised interact with a first and a second antibody heavy chain polypeptide to form an antigen-binding domain for a first and a second antigen, respectively, despite structural similarity or identity between the light chain polypeptides, the light chain polypeptides necessarily function differently as part of the bispecific antibody, since specificities of the different arms of the antibody differ. Consequently, there is no correlation between any one particularly identifying and substantial structural feature and any one particularly identifying functional feature (e.g., binding specificity). Therefore, absent a detailed description of at least a substantial number of the members of the genus of variable light chain polypeptides that have a common sequence but function differently, the supporting disclosure would not reasonably convey to the skilled artisan that Applicant has possession of the claimed invention.

Claims 61, 77, and 85 recite that the light chain polypeptides have the same sequence (i.e., the two light chain polypeptides of which the bispecific antibody is comprised are identical). However, because by definition the bispecific antibody binds two different antigens, the light chains of which the antibody is comprised necessarily function differently, regardless of their identical structure; so, there is still no correlation between any one particularly identifying and substantial structural feature and any one particularly identifying functional feature (e.g., binding specificity). Therefore, absent a detailed description of at least a substantial number of the members of the genus of variable light chain polypeptides that have an identical structure but function differently, the supporting disclosure would not reasonably convey to the skilled artisan that Applicant has possession of the claimed invention.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (*supra*) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

The supporting disclosure of the instant claims is not sufficient to meet the written description requirement set forth under 35 U.S.C. § 112, first paragraph, because the genus of bispecific antibodies to which the claims are directed are comprised of light chain polypeptides that differ both structurally and functionally, which precludes the skilled artisan from immediately envisioning, recognizing, or distinguishing at least most members of the genus. Because the two different arms of the bispecific antibodies do not necessarily retain the binding specificities of the antibodies comprising light chain polypeptides that are similar or identical to the bispecific antibodies' light chain

polypeptides, the bispecific antibodies possess *any* binding specificity, not necessarily the binding specificities of the "parent antibodies". Accordingly, as explained above, there is no correlation between the presence of "a common sequence", or an amino acid sequence that is at least 98% identical to the amino acid sequence of other light chain polypeptides and any one particularly identifying functional feature (e.g., binding specificity).

To the contrary, however, the supporting disclosure *would be sufficient* to adequately describe a method for preparing a bispecific antibody comprising a first and a second light chain polypeptide that is at least 98% identical to the light chain polypeptides of a first and a second antibody that binds a first and a different second antigen, wherein said first and second light chain only differ from the other at positions outside the CDRs and wherein said bispecific antibody retains the ability to bind both the first and second antigen, since, in such instances, *a correlation necessarily exists* between a recited structural feature that is common to both light chain polypeptides of the genus of light chain polypeptides of which the bispecific antibodies are comprised and specific functional features attributable to the presence of those common structural features.

Suggested Remedy:

Appreciating that it is should not actually be necessary to describe each and every light chain of each and every bispecific antibody that can be produced using the disclosed invention, it is suggested that Applicant remedy this issue by amending the claims to recite that the bispecific antibody retains the binding specificity of two antibodies that bind different antigens, which each comprise a light chain having a variable domain that is at least 98% identical to the light chain of the other antibody and differs from the other only at positions outside the CDRs. Furthermore, the claims should be amended to recite additional process steps including the functional antigen-specific screening of a phage display library comprised of antibodies comprising a plurality of heavy chain polypeptides and one or more variable light chain polypeptides having amino acid sequences that are at least 98% identical, the isolation of identified phage comprising nucleic acid encoding antigen-specific antibodies, and the cloning of

the encoding nucleic acid into an expression vector for expression in a host cell, and introducing the expression vector into the host cell.

11. Claims 52-54, 58-63, 66-71, 74-79, and 82-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for preparing a bispecific antibody comprising a first and a second heavy chain polypeptide and a light chain polypeptide that is capable of interacting with said first and second heavy chain polypeptides to form different antigen-biding sites that bind a first and a different second antigen, wherein said bispecific antibody binds both said first and different second antigen, said method comprising antigen-specific screening of a phage display library comprised of "parent" antibodies comprising a plurality of heavy chain polypeptides and a variable light chain polypeptide, identifying two "parent" antibodies having binding specificity for a first and a different second antigen, isolating the identified phages comprising a nucleic acid encoding said antigen-specific "parent" antibodies, cloning the encoding nucleic acids from the isolated phages into an expression vector to express in a host cell of a bispecific antibody comprising a first arm having the binding specificity of the first "parent" antibody for said first antigen and a second arm having the binding specificity of the second "parent" antibody for said different second antigen, introducing the expression vector into the host cell, culturing the host cell such that the nucleic acid encoding the bispecific antibody is expressed, and recovering the bispecific antibody from the host cell culture, **does not reasonably provide enablement for using** a method for preparing a bispecific antibody comprising a variable light chain polypeptide selected to have a common sequence or having at least 98% identity to the other variable light chain polypeptide of the bispecific antibody, which may, but not necessarily differ from the other only at positions outside the CDRs, said method comprising culturing a host cell comprising a nucleic acid encoding the variable light chain polypeptide and a first and second "variable heavy chain polypeptide" such that the nucleic acid is expressed and recovering the bispecific antibody. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 56, 57, 64, 65, 72, 73, 80, and 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making** a host cell comprising a nucleic acid encoding a bispecific antibody comprising a first and a second heavy chain polypeptide and a light chain polypeptide that is capable of interacting with said first and second heavy chain polypeptides to form different antigen-biding sites that bind a first and a different second antigen, wherein said bispecific antibody binds both said first and different second antigen, **does not reasonably provide enablement for making** a host cell comprising a nucleic acid encoding a bispecific antibody comprising a variable light chain polypeptide selected to have a common sequence or having at least 98% identity to the other variable light chain polypeptide of the bispecific antibody, which may, but not necessarily differ from the other only at positions outside the CDRs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This is a "scope of enablement rejection".

Claims 52-54, 58-63, 66-71, 74-79, and 82-87 are drawn to methods for producing a bispecific antibody comprising culturing a host cell comprising a nucleic acid encoding the bispecific antibody and recovering the bispecific antibody; claims 56, 57, 64, 65, 72, 73, 80, and 81 are drawn to host cells comprising nucleic acid encoding a bispecific antibody.

The amount of guidance, direction, and exemplification set forth in the specification would not sufficient to enable the skilled artisan to make and use the claimed invention without first having to perform an undue amount of additional experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the

presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are directed to a host cell or a process comprising culturing such a host cell, wherein the host cell comprises a nucleic acid molecule encoding a first polypeptide, a second polypeptide, and variable light chain polypeptide, wherein said first polypeptide comprises a first antibody heavy chain variable region and a first "multimerization domain", said second polypeptide comprises a second antibody heavy chain variable region and a second "multimerization domain", said first and second multimerization domains of said first and second polypeptides interact, and the variable light chain polypeptide interacts with the first antibody heavy chain variable domain or a second antibody heavy chain polypeptide to from an antigen-binding domain for a first and a different second antigen, respectively.

As explained above in the "written description rejection", the claims are directed to a genus of bispecific antibodies that comprise a light chain polypeptide that varies structurally and functionally. Moreover, there is no common structural feature of the light chain polypeptides of which the bispecific antibodies are comprised that correlates with any shared functional feature, since the bispecific antibodies bind *any* two antigens without necessarily retaining the binding specificities of two "parent" antibodies.

However, if the bispecific antibody does not have or retain the binding specificities of two antibodies comprising light chain polypeptides that share a common sequence with, or have at least 98% identity to the light chain polypeptides of the bispecific antibody, the skilled artisan could not use the bispecific antibody without performing undue experimentation to determine the binding specificity of the bispecific antibody prepared using the claimed invention and therefore could not make or use the claimed invention without undue experimentation. Although the methodology used to determine the binding specificity of an antibody may be simple, the binding specificities of a bispecific antibody cannot be determined "blindly" without undue experimentation because of the sheer magnitude of the number of different antigens that might be recognized by the antibody. Only if the bispecific antibody produced using the claimed

invention has or retains the known binding specificities of antibodies comprising light chain polypeptides that share a common sequence with, or have at least 98% identity to the light chain polypeptides of the bispecific antibody could the skilled artisan use the claimed invention without having to first determine the binding specificities of the bispecific antibody and thus use the claimed invention without undue experimentation.

Furthermore, the skilled artisan cannot predict which two light chain antibodies have a common sequence or have at least 98% identity to one another, differing only at positions outside the CDRs, since such a determination can only be made by determining and comparing the amino acid sequences of each and every light chain of an enormous genus of antibodies. Moreover, the skilled artisan cannot "select" light chains having a common sequence or having at least 98% identity to one another and differing only at positions outside the CDRs, without predetermined knowledge of the amino acid sequences of the light chains of the enormous genus of known antibodies. Having to first determine and compare the amino sequences of the light chains of such an enormous genus of known antibodies would constitute undue experimentation.

Yet, notably the claims are not limited to methods for preparing bispecific antibodies, or host cells encoding such bispecific antibodies, which have light chain polypeptides that differ only at positions outside the CDRs:

Claims 52-57 and 66-72 are directed to a genus of bispecific antibodies having nondescript and varying binding specificities that comprise variable light chain polypeptides comprising a "common sequence", which is "an approximation" of that of the light chains polypeptides of two different antibodies having distinct binding specificities. Each light chain polypeptide may differ at virtually any position, including those positions within the CDRs.

Claims 82-84, 86, and 87 recite that a light chain polypeptide of the bispecific antibody is at least 98% identical to each light chain polypeptide of two different antibodies having unique binding specificities but may otherwise differ at any position, including those positions within the CDRs.

Claims 58-60, 62-65, 74-76, and 78-81, reciting that the light chain polypeptides of the bispecific antibody are 98% identical to each other or 98% identical to both the

light chain polypeptides of two different antibodies having unique binding specificities and in either event, *differ from one another at amino acid positions outside the CDRs*, do not require the light chains to comprise the same CDRs, since the light chain polypeptides may still vary within the CDRs. In other words, these claims do not recite that the light chain polypeptides vary from the others *only* at positions outside the CDRs and therefore may vary within the CDRs.

For reasons explained in detail below, the amount of guidance, direction, and exemplification provided in the specification is not sufficient to enable the skilled artisan to make *de novo* light chain polypeptides that are at least 98% identical to each other and *differ at positions within the CDRs*, which are functionally equivalent and can substitute from one another in forming distinct antigen-binding sites upon interacting with different heavy chain polypeptides. In other words, the specification does not teach the skilled artisan to make a "promiscuous" light chain polypeptide that can interact with different heavy chain polypeptides to form antigen-binding sites that bind distinct antigens; rather, the specification merely teaches that it is possible to isolate antibodies comprising the same light chain but which have different binding specificities.

Even if the light chain polypeptides were to differ only at positions outside the CDRs, the skilled artisan still could not make or use the claimed invention without undue experimentation, since the skilled artisan cannot predict which two light chain antibodies that have been determined to have a common sequence or have at least 98% identity to one another, differing only at positions outside the CDRs, can be used to produce a bispecific antibody having any particular dual binding specificity unless it is first determined if different antibodies comprising such light chains have the sought-after binding specificity of one or the other arm of the bispecific antibody. Moreover, the skilled artisan cannot "select" light chains having a common sequence or having at least 98% identity to one another and differing only at positions outside the CDRs, which will function in a bispecific antibody having any particular dual binding specificity without predetermined knowledge of ability of the light chains to function in antibodies having the particular binding specificity of one or the other arm of the bispecific antibody. Having to first determine which light chains that *have* a common sequence or *have* at

least 98% identity to one another, differing only at positions outside the CDRs, can be used to produce a bispecific antibody having a particular dual binding specificity by assembling a large plurality of bispecific antibodies using such light chains and then determining which of the plurality has the sought-after dual binding specificity would constitute undue experimentation.

The specification, however, does disclose a method for producing a bispecific antibody comprising a first and a second light chain polypeptide that is identical to the light chain polypeptides of a first and a second antibody that binds a first and a different second antigen, wherein said first and second light chain polypeptides only differ from the other at positions outside the CDRs and wherein said bispecific antibody retains the ability to bind both said first and different second antigen. This disclosed method comprises the following steps:

(a) Antigen-specific screening of a phage display library comprised of "parent" antibodies comprising a plurality of heavy chain polypeptides and a variable light chain polypeptide;

(b) Identifying two "parent" antibodies having binding specificity for a first and a different second antigen;

(c) Isolating the identified phages comprising a nucleic acid encoding said antigen-specific "parent" antibodies;

(d) Cloning the encoding nucleic acids from the isolated phages into an expression vector to express in a host cell of a bispecific antibody comprising a first arm having the binding specificity of the first "parent" antibody for said first antigen and a second arm having the binding specificity of the second "parent" antibody for said different second antigen;

(e) Introducing the expression vector into the host cell, culturing the host cell such that the nucleic acid encoding the bispecific antibody is expressed; and

(f) Recovering the bispecific antibody from the host cell culture.

This disclosed method circumvents the need to predetermine the amino acid sequences of each and every light chain polypeptide and then determine if the light chains that have a common sequence or are at least 98% identical, and may or may not differ only

at positions outside the CDRs, can be used to produce a bispecific antibody having any particular sought-after dual binding specificity, since one would in the process determine and select a light chain polypeptide that has the dual function of interacting with two different heavy chain polypeptides to form antigen-binding domains that bind distinct antigens and which would be reasonably expected to function in a bispecific antibody comprising the light chain polypeptide and both heavy chain polypeptides that has or retains the ability to bind both antigens.

If, more than one light chain polypeptide, which differ structurally, were to be used in constructing the phage display library, it would first be necessary to identify more than one light chain polypeptide that have a common sequence or are at least 98% identical, and may or may not differ only at positions outside the CDRs. Then, it would be necessary to identify and isolate the phage encoding an antibody that binds to a particular antigen and subsequently determine whether the light chain of that antibody is capable of also forming an antigen-binding site capable of binding a second antigen. It is submitted that it would be merely serendipitous to discover a light chain capable of such a dual function. Alternatively, the phage display library could be screened to identify phage encoding two different antibodies that have the desired antigen-binding specificities; however, unless it was fortuitously discovered that both antibodies comprise the same light chain, it would be necessarily to determine if the light chain of either antibody is capable of functionally replacing the other, because, despite having a common sequence or even having at least 98% identity, the skilled artisan cannot predict the consequence of the amino acid differences in determining the ability of the different light chains to interact functionally with different heavy chain polypeptides to form antigen-binding sites for distinct antigens.

Mariuzza et al. (*Annu. Rev. Biophys. Biophys. Chem.* 1987; **16**: 139-159) reviews the structural basis of antigen-antibody recognition is reviewed. A naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the

amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

While the prior art teaches some understanding of the structural basis of antigen-antibody recognition, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA.* 1987 May; **84** (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA.* 1989 Jul; **86** (14): 5532-5536) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions as a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

Thus, because of the unpredictable consequences of amino acid substitutions, insertions, and deletions in the primary structure of an antibody or portion thereof, the effects of such alterations in the structure of an antibody must be tested empirically before an antibody can be used, and therefore, although the relative skill of those in the art is high, undue experimentation would be necessary before the claimed invention, commensurate in scope with the claims, could be made and used.

In addition, despite the fact that the prior art, for example, teaches a few examples of functionally distinct antibodies that comprise the *same* light chain polypeptide, it is submitted that rarely would one expect to find antibodies that comprise structurally different light chains, which are functionally equivalent despite the structural differences, and particularly where those differences occur in the CDRs. As explained above, most of the amino acids of the light chain that contact the antigen are positioned within one of three CDRs; while only two amino acids outside these regions, in the so-called "framework" contact the antigen. It is by virtue of differences in the CDRs and more generally in the so-called "variable region" of the light chain and heavy chain polypeptides that the immune system is capable of producing such a vast repertoire of antibodies that bind different antigens. In other words, the differences that occur in the primary structures of antibodies actually promote differences in binding specificity; so, again, it would not be reasonably expected that two structurally different light chain polypeptides would be functionally equivalent or capable of interacting with two different heavy chain polypeptides to produce different antigen-binding sites that bind particular antigens, which are structurally distinct. Gulliver et al. (*J. Biol. Chem.* 1994; **269** (39): 24040-24405) (of record), for example, teaches two functionally distinct antibodies that have light chain polypeptides comprising nearly identical amino acid sequences; see entire document (e.g., the abstract). However, despite having nearly identical primary structures, Gulliver et al. teaches the shape of the antigen-binding site of the different antibodies are distinctly different, as might be expected, since the antibodies bind antigens that differ markedly in structure (abstract). Accordingly, it is submitted that the skilled artisan would not be reasonably expected two structurally different light chain polypeptides to be functionally equivalent or capable of interacting with two different heavy chain polypeptides to produce different antigen-binding sites that bind particular antigens, which are structurally distinct. Consequently, the skilled artisan could not make or use the claimed invention without undue experimentation, since it would be necessary in every instance to first determine if two light chain polypeptides comprising a common sequence or having at least 98% identity can substitute for one another in different antigen-binding sites before the invention can be used to produce a bispecific

antibody comprising such different light chain polypeptides that has any particular dual binding specificity.

Finally, it is duly noted that the prior art teaches engineering recombinant bispecific antibodies by grafting CDRs of murine antibodies into common or consensus human antibody frameworks; see, e.g., Shalaby et al. (*J. Exp. Med.* 1992 Jan; **175**: 217-225). Such "humanized" bispecific antibodies comprise light chain polypeptides that have common sequences (see the art rejection set forth below); yet, because the light chain polypeptides of the different arms of the bispecific antibody comprise different CDRs, the light chain polypeptides are unlikely to be at least 98% identical to one another. However, because the CDRs of the different light chain polypeptides vary, it would not be reasonably expected that the different light chains are functionally equivalent or capable of substituting for the other without loss of the dual binding specificity of the bispecific antibody. Furthermore, the prior art (Vaughan et al. and Reddy et al. (both of record)) suggests preparing bispecific antibodies comprising light chain polypeptides that are identical. However, unless the prior art teaches antibodies comprising identical light chains that bind distinct antigens, the skilled artisan cannot know or predict which antibodies having any particular binding specificity will comprise light chain polypeptides that are identical to those of other antibodies having a different binding specificity; so, as explained above, undue experimentation would be required to make or use the claimed invention because it would be purely fortuitous to find two such antibodies having the sought-after binding specificities of the desired bispecific antibody. In addition, the prior art teaches bispecific antibodies that actually do have the same or nearly identical light chain polypeptides, despite their functional differences; see, e.g., Mallender et al. (of record). Again, although the skilled artisan is enabled for making and using host cells encoding these disclosed antibodies, since the prior art teaches making and using the antibodies, it is submitted that antibodies having different binding specificities do not typically have light chain polypeptides that are 98% identical, and more particularly do not typically differ only at positions outside their respective CDRs, and the skilled artisan would not reasonably expect, nor predict that structurally

distinct light chain polypeptides are functionally equivalent in a bispecific antibody having any particular dual binding specificity.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to make or use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

12. Claims 52, 55, 56, 66, 71, and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Mallender et al. (*Journal of Biological Chemistry.* 1994; **269**: 199-206) (of record), as evidenced by Gulliver et al. (*Journal of Biological Chemistry.* 1994; **269**: 7934-7940) (of record).

Claims 52, 55, 66, and 71 drawn to a method for making a bispecific antibody, wherein said method comprises culturing a host cell comprising a nucleic acid molecule encoding a first polypeptide, a second polypeptide, and a variable light chain polypeptide and recovering the bispecific antibody produced by the cell, wherein said first polypeptide comprises a first antibody heavy chain variable region and a first "multimerization domain", said second polypeptide comprises a second antibody heavy chain variable region and a second "multimerization domain", said first and second multimerization domains of said first and second polypeptides interact, and the variable light chain polypeptide interacts with the first antibody heavy chain variable domain or a second antibody heavy chain polypeptide to from an antigen-binding domain for a first and a different second antigen, respectively.

It is noted that claims 52 and 66 recite, "each variable light chain polypeptide is selected to have a common sequence" or "the variable light chain polypeptide is selected to have a common sequence from a first antibody variable light chain specific for a first antigen and from a second antibody variable light chain specific for a second antigen"; however, these recitations do not appear to be active steps of which the claimed processes are comprised, since the only active steps recited in the bodies of

the claims are (a) culturing a host cell and (b) recovering the bispecific antibody. Moreover, it is recognized that the recitation is the intended rationale to be used in selecting the light chain polypeptides of the bispecific antibody produced by the claimed process, but the rationale used to select the light chain polypeptides does not materially, structurally, or functionally limit the product produced by the process.

Claims 56 and 72 are drawn to a host cell comprising a nucleic acid molecule encoding a first polypeptide, a second polypeptide, and a variable light chain polypeptide, wherein said first polypeptide comprises a first antibody heavy chain variable region and a first "multimerization domain", said second polypeptide comprises a second antibody heavy chain variable region and a second "multimerization domain", said first and second multimerization domains of said first and second polypeptides interact, and the variable light chain polypeptide interacts with the first antibody heavy chain variable domain or a second antibody heavy chain polypeptide to from an antigen-binding domain for a first and a different second antigen, respectively.

It is noted that claims 56 and 72 recite, "each variable light chain polypeptide is selected to have a common sequence" or "the variable light chain polypeptide is selected to have a common sequence from a first antibody variable light chain specific for a first antigen and from a second antibody variable light chain specific for a second antigen"; however, the claims are drawn to a product and the rationale used in selecting the light chain polypeptides to produce the product does not materially, structurally, or functionally limit the product.

The specification discloses that "a multimerization domain" is "a region of each of the polypeptides of the heteromultimer", which "promotes the stable interaction of the chimeric molecules within the heteromulitmer complex" and/or which "promotes interaction between a specific first polypeptide and a specific second polypeptide" (page 19, line 27, to page 20, line 2). Furthermore, the specification discloses: "The multimerization domains may interact via an immunoglobulin sequence, leucine zipper, a hydrophobic region, a hydrophilic region, or a free thiol which forms an intermolecular disulfide bond between the chimeric molecules of the chimeric heteromultimer" (page

20, lines 5-9). Notably, the specification does not exclude multimerization domains that interact via a covalent or more particularly, a peptide bond.

Mallendar et al. teaches a method for preparing a bispecific antibody; see entire document, particularly the abstract. Mallendar et al. discloses selecting the light chain polypeptides of a first and second antibody, wherein the first and second antibody, namely SCA 4-4-20 and SCA 04-01 bind different antigens, namely fluorescein and single-stranded DNA, respectively (abstract). Mallendar et al. teaches culturing a host cell comprising a nucleic acid encoding a first polypeptide that comprises a first antibody variable heavy chain domain, a second polypeptide that comprises a second antibody variable heavy domain, and the selected variable light chain polypeptides; see, e.g., page 200, column 2. Mallendar et al. teaches that the first and second polypeptides comprise a portion of a flexible linker that covalently joins the first and second polypeptides (abstract), which, in light of the specification, is deemed the same as a "multimerization domain", since the portions of the linker contained in the first and second polypeptides "interact to form a bispecific antibody". Mallendar et al. teaches recovering the bispecific antibody from the cell culture; see, e.g., page 200, column 2.

As evidenced by **Gulliver et al.**, the primary structures (i.e., the amino acid sequences) of the light chain polypeptides of SCA 4-4-20 and SCA 04-01 are "nearly identical" (abstract). As evidenced by Applicant's remark at page 12, paragraph 2, of the amendment filed September 25, 2003: nearly identical light chains have at least 98% identity. Accordingly, the light chain polypeptides of SCA 4-4-20 and SCA 04-01 comprise a common sequence and, moreover, are deemed to have at least 98% identity.

Absent a showing of any difference, the first and second "multimerization domains" of the bispecific antibody of the prior art each comprise a hydrophilic region and a hydrophobic region, since it comprises amino acids that are "hydrophilic" or "hydrophobic"; see Figure 1 at page 200. Nonpolar amino acids, such as phenylalanine, are relatively hydrophobic, whereas polar and charged amino acids are relatively hydrophilic.

Claim Rejections - 35 USC § 103

13. Claims 52-57, 66-68, and 71-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shalaby et al. (*J. Exp. Med.* 1992 Jan; **175**: 217-225), as evidenced by Carter et al. (*Proc. Natl. Acad. Sci. USA.* 1992 May; **89**: 4285-4289), in view of Zhu et al. (*Protein Science* 1997; **6**: 781-788) (of record).

Claims 52-55 and 66-71 drawn to a method for making a bispecific antibody, wherein said method comprises culturing a host cell comprising a nucleic acid molecule encoding a first polypeptide, a second polypeptide, and a variable light chain polypeptide and recovering the bispecific antibody produced by the cell, wherein said first polypeptide comprises a first antibody heavy chain variable region and a first "multimerization domain", said second polypeptide comprises a second antibody heavy chain variable region and a second "multimerization domain", said first and second multimerization domains of said first and second polypeptides interact, and the variable light chain polypeptide interacts with the first antibody heavy chain variable domain or a second antibody heavy chain polypeptide to from an antigen-binding domain for a first and a different second antigen, respectively. Claims 53-55, 68, and 71 recite that the first and second polypeptides each comprise an antibody constant region, or more particularly an antibody constant region from a C_H3 domain or from an IgG, and the multimerization domains comprise an immunoglobulin sequence, a leucine zipper, a hydrophobic region, a hydrophilic region, a protuberance-into-cavity interaction, or a free thiol that forms an intermolecular disulfide bond.

It is noted that claims 52 and 66 recite, "each variable light chain polypeptide is selected to have a common sequence" or "the variable light chain polypeptide is selected to have a common sequence from a first antibody variable light chain specific for a first antigen and from a second antibody variable light chain specific for a second antigen"; however, these recitations do not appear to be active steps of which the claimed processes are comprised, since the only active steps recited in the bodies of the claims are (a) culturing a host cell and (b) recovering the bispecific antibody. Moreover, it is recognized that the recitation is the intended rationale to be used in selecting the light chain polypeptides of the bispecific antibody produced by the claimed

process, but the rationale used to select the light chain polypeptides does not materially, structurally, or functionally limit the product produced by the process. Accordingly, claims 52-55 and 66-71 are drawn to a method for preparing a bispecific antibody comprising light chain polypeptides that have a common sequence.

Claims 56, 57, 72, and 73 are drawn to a host cell or more particularly, a mammalian host cell comprising a nucleic acid molecule encoding a first polypeptide, a second polypeptide, and a variable light chain polypeptide, wherein said first polypeptide comprises a first antibody heavy chain variable region and a first "multimerization domain", said second polypeptide comprises a second antibody heavy chain variable region and a second "multimerization domain", said first and second multimerization domains of said first and second polypeptides interact, and the variable light chain polypeptide interacts with the first antibody heavy chain variable domain or a second antibody heavy chain polypeptide to from an antigen-binding domain for a first and a different second antigen, respectively.

It is noted that claims 56 and 72 recite, "each variable light chain polypeptide is selected to have a common sequence" or "the variable light chain polypeptide is selected to have a common sequence from a first antibody variable light chain specific for a first antigen and from a second antibody variable light chain specific for a second antigen"; however, the claims are drawn to a product and the rationale used in selecting the light chain polypeptides to produce the product does not materially, structurally, or functionally limit the product. Accordingly, claims 56, 57, 72, and 73 are drawn to a host cell comprising a nucleic acid encoding a light chain polypeptides that have a common sequence.

Shalaby et al. teaches a method for making a bispecific antibody that comprises an arm that binds CD3 and an arm that binds HER2; see entire document (e.g., the abstract). Shalaby et al. teaches the process comprised humanizing the light and heavy chain variable domains polypeptides of a murine monoclonal antibody by gene conversion mutagenesis, as taught by Carter et al. (page 219, column 2). Shalaby et al. teaches the bispecific antibody targets cytotoxic T cells expressing CD3 to HER2-

overexpressing cancer cells and therefore has potential use as a therapeutic agent for the treatment of cancer (abstract).

As evidenced by **Carter et al.**, the humanized anti-CD3 light chain polypeptide has a common sequence with the humanized anti-HER2 light chain polypeptide and, moreover, the light chain polypeptides share substantially the same framework and for the most part, only differ from one another within their respective CDRs; see entire document, particularly Figure 1 at page 4286. Compare Figure 1 at page 4286 of Carter et al. to Figure 1 at page 220 of Shalaby et al.

Shalaby et al. teaches direct chemical coupling of fragments of the anti-CD3 and anti-HER2 antibodies to produce the bispecific antibody; however, Shalaby et al. does not teach that bispecific antibodies can be prepared by expressing in a host cell a nucleic acid encoding a first polypeptide, a second polypeptide, and a variable light chain polypeptide and recovering the bispecific antibody produced by the cell, wherein said first polypeptide comprises a first antibody heavy chain variable region and a first "multimerization domain", said second polypeptide comprises a second antibody heavy chain variable region and a second "multimerization domain", said first and second multimerization domains of said first and second polypeptides interact, and the variable light chain polypeptide interacts with the first antibody heavy chain variable domain or a second antibody heavy chain polypeptide to from an antigen-binding domain for a first and a different second antigen, respectively.

Zhu et al. teaches methods for producing bispecific antibodies; see entire document. More specifically, Zhu et al. teaches bispecific antibodies can be prepared by expressing in a host cell a nucleic acid encoding a first polypeptide, a second polypeptide, and a variable light chain polypeptide and recovering the bispecific antibody produced by the cell, wherein said first polypeptide comprises a first antibody heavy chain variable region and a first "multimerization domain", said second polypeptide comprises a second antibody heavy chain variable region and a second "multimerization domain", said first and second multimerization domains of said first and second polypeptides interact, and the variable light chain polypeptide interacts with the first antibody heavy chain variable domain or a second antibody heavy chain

polypeptide to from an antigen-binding domain for a first and a different second antigen, respectively; see entire document (e.g., Figure 1 at page 782; page 785, column 2; page 786, column 2, through page 787, column 1). Moreover, Zhu et al. compares two engineering strategies for producing bispecific antibodies, each of which enhance the formation of functional bispecific antibodies; see, e.g., page 785, column 1. Zhu et al. teaches the strengths, as well as the limitations associated with both approaches (page 785, column 2). The first approach involves the installation of non-naturally occurring cysteine residues, which form antibody-stabilizing disulfide bonds; see, e.g., the abstract. Zhu et al. teaches this first approach eliminates the undesirable production of higher order aggregates and mulitmers and increases the immunoreactive fraction, as compared to the conventional approach that does not involve engineering additional disulfide bonds (page 785, column 2). Zhu et al. teaches an additional attractive feature of the engineered disulfide-stabilized antibody is that it can be distinguished from other species by SDS-PAGE (page 785, column 2). Zhu et al. teaches the major drawback of this first approach is the very low yield of soluble protein, but also Zhu et al. discloses engineering a disulfide bond across the C_H3 domain interface of an antibody can facilitate heterodimerization without compromising expression titers from human (mammalian) embryonic kidney cells (page 785, column 2). Even so, Zhu et al. discloses the fraction of recovered disulfide-stabilized antibody that was functional following expression in *E. coli* was improved, as compared to the fraction of recovered diabody produced by the conventional methodology (abstract). The second strategy used by Zhu et al. is the so-called "knobs-into-holes" engineering approach, which involves making sterically complementary mutations to install a protuberance and a corresponding cavity; see, e.g., page 785, column 1. Zhu et al. teaches amino acid replacements at either interface to create a protuberance and a complementary cavity are sufficient to improve the fraction of functional bispecific antibody, while maintaining overall recoverable yields and affinity for the antigens close to that of the antibody produced by the conventional methodology (abstract).

It would have been *prima facie* obvious to one ordinarily skilled in the art to produce humanized bispecific antibody having dual binding specificity for HER2 and

CD3 using the methodology taught by Zhu et al. and the humanized antibodies of Shalaby et al., because Shalaby et al. teaches such a bispecific antibody has potential use as a therapeutic agent for the treatment of cancer and Zhu et al. teaches methods for recombinantly producing a bispecific antibody from the antibodies of Shalaby et al., which results in products having relatively increased stability and relatively higher yields, as compared to bispecific antibodies produced by other more conventional methodology. One ordinarily skilled in the art would have been motivated at the time of the invention to do so because the bispecific antibody can be used in accordance with the teachings of Shalaby et al. to target cytotoxic T cells expressing CD3 to HER2-overexpressing cancer cells.

14. Claims 52-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reddy et al. (*Anticancer Research.* 1993; **13**: 2077-2083) (of record), Vaughan et al. (*Nature Biotechnology.* 1996; **14**: 309-314) (of record), and Zhu et al. (*Protein Science.* 1997; **6**: 781-788) (of record).

Claims 52-55, 58-63, 66-71, 74-79, and 82-87 drawn to a method for making a bispecific antibody, wherein said method comprises culturing a host cell comprising a nucleic acid molecule encoding a first polypeptide, a second polypeptide, and a variable light chain polypeptide and recovering the bispecific antibody produced by the cell, wherein said first polypeptide comprises a first antibody heavy chain variable region and a first "multimerization domain", said second polypeptide comprises a second antibody heavy chain variable region and a second "multimerization domain", said first and second multimerization domains of said first and second polypeptides interact, and the variable light chain polypeptide interacts with the first antibody heavy chain variable domain or a second antibody heavy chain polypeptide to from an antigen-binding domain for a first and a different second antigen, respectively. Claims 53-55, 68, and 71 recite that the first and second polypeptides each comprise an antibody constant region, or more particularly an antibody constant region from a C_H3 domain or from an IgG, and the multimerization domains comprise an immunoglobulin sequence, a leucine

zipper, a hydrophobic region, a hydrophilic region, a protuberance-into-cavity interaction, or a free thiol that forms an intermolecular disulfide bond.

It is noted that claims 52 and 66 recite, "each variable light chain polypeptide is selected to have a common sequence" or "the variable light chain polypeptide is selected to have a common sequence from a first antibody variable light chain specific for a first antigen and from a second antibody variable light chain specific for a second antigen"; claim 58, recites, "each variable light chain polypeptide [...] is selected to have at least 98% sequence identity with the other variable light chain of the bispecific antibody [which] differ from one another at amino acid positions outside the CDRs"; and claim 74 recites, "the variable light chain [...] is selected to have at least 98% identity to a first antibody variable light chain specific for a first antigen and to a second antibody variable light chain specific for a second antigen". However, these recitations do not appear to be active steps of which the claimed processes are comprised, since the only active steps recited in the bodies of the claims are (a) culturing a host cell and (b) recovering the bispecific antibody. Moreover, it is recognized that the recitation is the intended rationale to be used in selecting the light chain polypeptides of the bispecific antibody produced by the claimed process, but the rationale used to select the light chain polypeptides does not materially, structurally, or functionally limit the product produced by the process. Accordingly, claims 52-55 and 66-71 drawn to a method for making a bispecific antibody comprising light chain polypeptides that have a common sequence, or a bispecific antibody comprising light chain polypeptides that are at least 98% identical to each other or at least 98% identical to the light chain polypeptides of two antibodies having different binding specificities and in either event, differing only at positions outside their respective CDRs.

Claims 82-87 recite the bispecific antibody comprises a light chain that is obtained by screening a library of antibody variable domains and selecting the variable light chain to have at least 98% sequence identity to each variable light chain domain of a first and second antibody that bind different antigens; however, this recitation is not a recitation of an active step. The only active steps recited in the body of claim 82 are (a) culturing a host cell and (b) recovering the bispecific antibody. Therefore, it is

recognized that the recitation is the intended method and rationale to be used in selecting the light chain polypeptides of the bispecific antibody produced by the claimed process, but the method and rationale used to select the light chain polypeptides do not materially, structurally, or functionally limit the product produced by the process. Claims 82-87 are drawn to a method for preparing a bispecific antibody comprising a light chain having at least 98% identity to each light chain polypeptide of two different antibodies having unique binding specificities.

Claims 56, 57, 64, 65, 72, 73, 80, and 81 are drawn to a host cell or more particularly, a mammalian host cell comprising a nucleic acid molecule encoding a first polypeptide, a second polypeptide, and a variable light chain polypeptide, wherein said first polypeptide comprises a first antibody heavy chain variable region and a first "multimerization domain", said second polypeptide comprises a second antibody heavy chain variable region and a second "multimerization domain", said first and second multimerization domains of said first and second polypeptides interact, and the variable light chain polypeptide interacts with the first antibody heavy chain variable domain or a second antibody heavy chain polypeptide to from an antigen-binding domain for a first and a different second antigen, respectively.

It is noted that claims 56 and 72 recite, "each variable light chain polypeptide is selected to have a common sequence" or "the variable light chain polypeptide is selected to have a common sequence from a first antibody variable light chain specific for a first antigen and from a second antibody variable light chain specific for a second antigen"; claim 64, recites, "each variable light chain polypeptide [...] is selected to have at least 98% sequence identity with the other variable light chain of the bispecific antibody [which] differ from one another at amino acid positions outside the CDRs"; and claim 80 recites, "the variable light chain [...] is selected to have at least 98% identity to a first antibody variable light chain specific for a first antigen and to a second antibody variable light chain specific for a second antigen". However, the claims are drawn to a product and the rationale used in selecting the light chain polypeptides to produce the product does not materially, structurally, or functionally limit the product. Accordingly, claims 56, 57, 72, and 73 are drawn to a host cell comprising a nucleic acid encoding a

light chain polypeptides that have a common sequence. Claims 64, 65, 80, and 81 are drawn to a host cell comprising a nucleic acid encoding a light chain polypeptides that are at least 98% identical to each other or at least 98% identical to the light chain polypeptides of two antibodies having different binding specificities and in either event, differing only at positions outside their respective CDRs.

Reddy et al. teaches a method for preparing a bispecific antibody for cancer therapy that comprises binding specificity for the tumor-associated antigen CEA and an anticancer agent, namely doxorubicin; see entire document (e.g., the abstract).

Vaughan et al. teaches a human antibody fragment with sub-nanomolar affinity that binds doxorubicin, namely VoDox-1; see entire document, particularly page 313, Table 3. Vaughan et al. discloses VoDox-1 was identified as having the highest affinity constant of the antibodies produced (page 311, column 1). Vaughan et al. teaches VoDox-1 comprises a light chain variable domain (V_L) identified as "L12a" (page 312, Table 2).

In addition, Vaughan et al. teaches a human antibody fragment with sub-nanomolar affinity that binds CEA, namely CEA-6 (page 313, Table 3, in particular). Vaughan et al. teaches CEA-6 was tested in flow cytometry with CEA+ HeLa cells and is shown to recognize CEA in the context of a cell surface, binding strongly and specifically (page 311, column 1). Vaughan et al. teaches CEA-6 has been used to immunolocalize CEA in tissue sections (page 312, column 2). Vaughan et al. discloses CEA-6 has a binding affinity of 7.7 nM (page 313, Table 3), which Vaughan et al. teaches compares favorably with CEA antibodies derived from rodent immunization (page 312, column 2). Vaughan et al. teaches the very high binding affinity of the antibody enables its direct use in a variety of bioassays (page 312, column 1). Furthermore, Vaughan et al. teaches slow off-rates are an important characteristic for antibodies used for human therapy (page 312, column 2). Vaughan et al. discloses CEA-6 has an off-rate of 6.2×10^{-3} s^{-1} (page 313, Tables 3 and 4). Vaughan et al. discloses that the best antibodies previously isolated from a large synthetic repertoire of Fab fragments were of high affinity but had relatively fast off-rates, whereas the antibodies derived from their library have a slower off-rate than either those from rodent

immune responses or scFvs from smaller libraries (page 312, column 2). Vaughan et al. teaches CEA-6 comprises a light chain variable domain (V_L) identified as "L12a" (page 312, Table 2).

Furthermore, Vaughan et al. teaches the main focus of investigators is to generate human antibodies for therapy, as it was well known that human antibodies provide numerous advantages over rodent antibodies (page 309, column 1). Vaughan et al. discloses their work indicates that neither immunization nor affinity maturation is a prerequisite for generating high affinity antibodies and the relative speed and ease with which antibodies with high affinities can be isolated from the scFv repertoire suggests conventional hybridoma technology may be superceded by large phage libraries in the production of high affinity human monoclonal antibodies (page 313, column 1).

Zhu et al. teaches that which is set forth above in section 12.

It would have been *prima facie* obvious to one ordinarily skilled in the art to produce a high-affinity human bispecific antibody having dual binding specificity for doxorubicin and CEA using the methodology taught by Zhu et al. and the scFv antibodies CEA-6 and VoDox-1 of Vaughan et al., because Reddy et al. teaches a therapeutically useful bispecific antibody having such dual binding specificity, but which is a rodent antibody, whereas Vaughan et al. teaches a human scFv antibody having high affinity, and a slow off-rate, with the specificity of one arm or the other of the antibody of Reddy et al., and Zhu et al. teaches methods for producing a bispecific antibody from the scFv antibodies of Vaughan et al., which results in products having relatively increased stability and relatively higher yields, as compared to bispecific antibodies produced by other more conventional methodology. One ordinarily skilled in the art would have been motivated at the time of the invention to do so because the bispecific antibody can be used in accordance with the teachings of Reddy et al. to target doxorubicin to CEA+ cancer cells in a subject.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 52-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30-43 and 45-55 of copending Application No. 09/373,403. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 30-38, 40-43, and 45-55 of copending Application No. 09/373,403 are drawn to a method for preparing a multispecific antibody or a host cell comprising a nucleic acid encoding a multispecific antibody, whereas the instant claims are drawn to a method for preparing a bispecific antibody or a host cell comprising a nucleic acid encoding a bispecific antibody. However, a bispecific antibody is obvious variant of a multispecific antibody. For example, monoclonal antibodies are typically IgG molecules, which are bivalent (i.e., comprise two antigen-binding sites and are thus capable of binding two antigen molecules). A multispecific bivalent antibody is necessarily bispecific. This conclusion is further strengthened by consideration of the supporting disclosure of the copending claims, which expressly defines the term "multispecific" as inclusive of "bispecific"; see, e.g., page 19, lines 1-15. Furthermore, the copending claims are drawn to different species of the claimed method for preparing a bispecific

antibody comprising engineering the bispecific antibody to comprise specific residues; see, e.g., claim 35. In contrast, the instant claims are drawn to more generic methods for preparing a bispecific antibody comprising engineering the antibody to have particular features but without specifying the specific residues that comprise those features. Accordingly, limitations in the copending claims anticipate the more generic limitations of the claims set forth in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 52-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 8-16 of copending Application No. 10/143,437. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-3 and 8-16 of copending Application No. 10/143,437 are drawn to a multispecific antibody or a method for preparing a multispecific antibody, whereas the instant claims are drawn to a method for preparing a bispecific antibody or a host cell comprising a nucleic acid encoding a bispecific antibody. However, as explained in section 16 above, a bispecific antibody is obvious variant of a multispecific antibody. This conclusion is further strengthened by consideration of the supporting disclosure of the copending claims, which expressly defines the term "multispecific" as inclusive of "bispecific"; see, e.g., page 19, lines 12-26. Furthermore, the copending claims are drawn to a species of the claimed method for preparing a bispecific antibody comprising introducing the nucleic acid encoding the first and additional polypeptide into the host cell; see, e.g., claim 11. In contrast, the instant claims do not recite the step of introducing the nucleic acid into the host cell. Additionally, the copending claims are drawn to a method for preparing a bispecific antibody that further comprises an immunoadhesin, whereas the instant claims are not. Accordingly, limitations in the copending claims anticipate the more generic limitations of the claims set forth in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. Claims 52-56 are directed to an invention not patentably distinct from claims 1-3 and 8-16 of commonly assigned copending Application No. 10/143,437. Specifically, although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth above in section 17.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/143,437, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Response to Amendment

19. Applicant's arguments traversing the grounds of rejection set forth in the previous Office action are acknowledged.

Regarding the rejection of claim 47 under 35 U.S.C. § 102(b) as being anticipated by Mallender et al., Applicant has stated that the cancellation of the claim has rendered the rejection of the claim moot. As claim 47 has been canceled, the

rejection of claim 47 set forth in section 10 of the previous Office action has been withdrawn.

Regarding the rejection of claims 30-51 under 35 U.S.C. § 103(a) as being unpatentable over Reddy et al., Vaughan et al. and Zhu et al., Applicant has argued the that cancellation of the rejected claims has rendered that ground of rejection moot. As claims 30-51 have been canceled, the rejection of those claims set forth in section 12 of the previous Office action has been withdrawn.

At pages 12-18 of the amendment filed December 17, 2004, Applicant has addressed the latter ground of rejection insofar as it might apply to the newly presented claims. It appears that Applicant has reiterated arguments that have already been set forth in replying to prior Office actions.

Applicant's arguments have again been carefully considered but not found persuasive for reasons that have already been stated in the Advisory Office action mailed October 28, 2004 and the Final Office action mailed June 17, 2004.

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 11, 2005